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BRIEF REPORT

Buspirone for the Treatment of Generalized Anxiety Disorder in Williams Syndrome: A Case Series

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Abstract

Co-morbid anxiety disorders, including generalized anxiety disorder (GAD), are highly prevalent among individuals with Williams syndrome (WS). However, reports of the pharmacologic treatment of only a limited number of previous anxiety disorders in WS have appeared in the literature. Here, we review the case histories of three adolescents/young adults with WS and the treatment course of co-morbid GAD with buspirone. Treatment with buspirone was well-tolerated and resulted in sustained response in all three cases. Common medical disorders in WS are highlighted with regards to safe and appropriate pharmacologic treatment of GAD. Buspirone's generally benign side effect profile is a major benefit of its use for treating GAD in individuals with WS.

Keywords Williams syndrome · Anxiety · Buspirone

Introduction

Williams syndrome (WS) is a complex multisystem disorder caused by a hemizygous microdeletion spanning 1.5 to 1.8 million base pairs which contains 26 to 27 genes at chromosome 7q11.23 (Ewart et al. 1993; Pober 2010). Multiple organ systems are affected by this microdeletion and there is a highly variable range and severity of cognitive and medical problems. Common phenotypic features and medical co-morbidities include a distinctive facies characterized as "pixie-like" in childhood but with coarser features in adulthood; cardiovascular disease (a so-called elastin arteriopathy), frequently manifesting as peripheral pulmonary stenosis, supravalvular aortic stenosis, and hypertension; connective tissue abnormalities; growth abnormalities; and endocrine problems including diabetes, subclinical hypothyroidism, early puberty, and hypercalcemia (Collins 2018; Kim et al. 2016; Morris 1993). Additional medical issues which commonly arise during infancy include low birth weight, feeding difficulties leading to poor weight gain, and hypotonia which can result in delayed motor milestones (Morris 1993). The prevalence of WS is estimated to be 1/7500 to 1/10,000 (Strømme et al. 2002).

The neurodevelopmental profile of WS includes delayed acquisition of motor and language milestones, a distinct cognitive profile typically with mild-to-moderate intellectual disability, and a unique personality. The average full-scale IQ among individuals with WS ranges from 40 to 100, with an average score of 50 to 60 (Martens et al. 2008). Relative cognitive strengths include auditory memory and language skills, while visuospatial skills tend to be weaker (Mervis et al. 2000). The personality of individuals with WS has been described as being very friendly, endearing, and sociable (Pober 2010). High rates of co-morbid psychopathology have been observed in WS. One study of 4 to 16-year-olds with WS found that on structured diagnostic interview, at least one *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), *4th Edition* diagnosis was found in 80.7% of children. The most prevalent diagnoses were attention-deficit/hyperactivity disorder (ADHD; 64.7%) and specific phobia (53.8%) (Leyfer et al. 2006).

Elevated rates of anxiety, fears, and phobias have been well documented in WS (Dykens 2003; Pober 2010). A

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meta-analysis on the prevalence of anxiety disorders in WS found that 48% of individuals with WS had at least one anxiety disorder. The most prevalent anxiety disorder was specific phobia. Common phobias identified included noise; blood, injury, or infection; thunderstorms; and lightning. The prevalence of generalized anxiety disorder (GAD) was approximately 10% (Royston et al. 2017). This meta-analysis also demonstrated that individuals with WS were more likely to have an anxiety disorder compared to individuals with a non-WS associated intellectual disability, RR 4.00, 95% CI 2.27–7.06 (Royston et al. 2017). A longitudinal study of anxiety in WS demonstrated that in the majority of cases, anxiety disorders persist over a 5-year follow-up period (62.2% overall, 74% phobia of loud noises, 63% other phobias). Furthermore, of the patients with at least one anxiety disorder, 72.2% developed additional anxiety disorders over time (Woodruff-Borden et al. 2010).

The high prevalence and persistence of anxiety in WS over the lifespan highlights the need for effective treatments. Unfortunately, there is a paucity of empirical evidence on psychopharmacologic treatment options for co-morbid psychopathology in WS. Here, we present the clinical histories and the use of buspirone, a serotonin $(5\text{-HT})_{1A}$ receptor partial agonist and dopamine (D3 and D4) antagonist (Bergman et al. 2013), in three adolescents/young adults with WS and co-morbid GAD.

Case 1

Ms. C is a 21-year-old female with WS confirmed via genetic testing which demonstrated only a single copy of the elastin gene. She was born at 39 weeks gestational age via C-section due to breech presentation. Her neonatal course was notable for mild jaundice and difficulty with feeding. Ms. C's developmental history included delayed acquisition of gross motor milestones and speech requiring extensive speech therapy. She began to walk at 2 years of age, intermittently engaged in toe walking, and demonstrated minimal pretend play. She received early intervention services, including speech therapy, physical therapy, occupational therapy, and play therapy. Her medical history was significant for chronic constipation and scoliosis. She has never had formal cognitive testing, however had attended specialized schools throughout her childhood with small class size and extensive speech and occupational therapy services. At the time of initial evaluation, she was attending a school for children and adolescents with disabilities as a partial residential student.

During the initial psychiatric evaluation at the age of 19 years, Ms. C and her parent reported a life-long history of anxiety with significant worsening around the age of 13 years. She experienced daily ruminative worries, with a particular fear of thunderstorms and loud noises. She checked the weather forecast multiple times per day and became hypervigilant whenever she saw clouds in the sky. Ms. C also had heightened anxiety during periods of academic stress and when she felt rushed. Additionally, she was experiencing somatic preoccupations about gastrointestinal (GI) symptoms including the sensation of nausea and the ability to pass a bowel movement in the setting of chronic constipation. She engaged in rectal picking behaviors to alleviate anxiety. There was no history of suicide attempts, self-injurious behaviors, or aggression. Ms. C was receiving individual cognitive behavior therapy (CBT) with an exposure basis to address her weather phobia, with mild to moderate improvement. There was a history of anxiety disorders on the paternal side of the family. Mental status exam was notable for facial dysmorphology consistent with WS and mild impairment of articulation, but a generally bright and appropriate affect.

Initial *DSM, 5th Edition* diagnoses of GAD and mild intellectual disability were made. Prior medication trials included citalopram (a selective serotonin reuptake inhibitor [SSRI]) up to 40 mg daily and lorazepam (a benzodiazepine) as needed for anxiety prior to blood draws. There was no appreciable improvement of anxiety on either of these medications. Furthermore, her rectal picking behaviors, constipation, and GI-related preoccupations worsened significantly when on citalopram. After the initial evaluation, buspirone was started at an initial dose of 2.5 mg twice daily and then gradually increased to 15 mg twice daily over a period of 7 weeks. At interval follow-up, Ms. C reported significant improvement in symptoms of GAD with fewer concerns about the weather, the ability to participate in noisy environments such as rock concerts, and fewer somatic worries (Table 1). Additionally, her constipation improved and she had fewer rectal picking behaviors. At her most recent follow up, 16 months after the initial evaluation, Ms. C reported ongoing and significant improvements in her anxiety symptoms. Her somatic concerns had fully resolved and she had minimal hypervigilance about the weather. She was attending a specialized vocational day program and was living at home. Overall, her improvement in anxiety was attributed to the combination of buspirone, completing a course of CBT, and behavioral strategies such as carrying noise cancelling headphones. No side effects were reported with buspirone treatment. Ms. C has continued to do well, with sustained improvement on a stable dose of buspirone, for the past 18 months.

Case 2

Ms. G is a 15-year-old female with WS confirmed via fluorescence in situ hybridization (FISH) genetic testing. She was born vaginally at 38 weeks gestational age after labor

Table 1 Change in symptoms of anxiety pretreatment and post-treatment with buspirone

	Anxiety manifestations	Areas of reported improvement	PARS	Buspirone dosage
Ms. C	Ruminative worries about thunderstorms and loud noises Checking weather forecast repeatedly Increased anxiety during academic stress and when being rushed Sensation of nausea/vomiting and fear of being able to pass bowel movement related to constipation; rectal picking	Minimal hypervigilance about the weather Ability to tolerate noisy environments, such as rock concerts Resolution of somatic worries Improved constipation and reduced rectal picking	Pretreatment: 25 Post-treatment: 7	15 mg twice daily
Ms. G	Anticipatory anxiety about loud sounds Ruminative worries about health of family and friends Difficulty with transitions Oppositionality and stubbornness Inattention	Seventy percent reduction in anxiety related to loud sounds, ruminative worry, and difficulty with transitions Near resolution of oppositionality and stubbornness Some improvement in inattention	Pretreatment: 23 Post-treatment: 6	7.5 mg thrice daily
Ms. M	Stressed facial expression Early morning awakening School avoidance Pacing	Relaxed facial expression Normalization of sleep duration Attending school without resistance Reduced pacing	Pretreatment: 19 Post-treatment: 6	10 mg twice daily

PARS Pediatric Anxiety Rating Scale, range 0–25

was induced due to concerns for being small for gestational age and moderate elevation of her mother's blood pressure. Her neonatal course was complicated by the presence of a nuchal cord and cyanotic spells. She had a brief stay in the neonatal intensive care unit where she was found to have a heart murmur, however was stable enough to be discharged home within 2 days. In terms of developmental milestones, she sat at 6 months, walked at 17 months, and was toilet trained at 3 years of age. Ms. G babbled and cooed normally, spoke her first word at 9 months of age, and put two to three words together into short phrases at 18 months of age. She had some toe walking. Her medical history was significant for recurrent otitis media resulting in myringotomy tube placement at 3 years of age, stable supravalvular aortic stenosis, bilateral inguinal hernia repair at 1 year of age, scoliosis repair at 11 years of age, and constipation. She was enrolled in her local public school where she received speech and occupational therapy, individual math classes, and a 1:1 aide.

During the initial assessment at the age of 8 years, Ms. G and her mother reported a high level of anxiety on several themes including anticipatory anxiety about loud sounds. She persistently avoided situations that might be noisy such as loud areas at camp and construction sites, was disproportionately concerned about the health of her family and friends, and struggled greatly with transitions. She had fingernail picking behaviors. Her mother reported that she could be oppositional and stubborn at times. Additionally, she had difficulty sustaining attention and staying on task at school. Family history was notable for panic disorder in her father treated with citalopram, mood and anxiety symptoms in her mother treated with sertraline (an SSRI), and anxiety in her maternal grandmother and great-aunt. Mental status exam was notable for good eye contact, clear and coherent speech, euthymic and reactive affect, inability to state the correct date, and a poor sense of danger. Ms. G's initial *DSM 5th Edition* diagnoses were GAD and mild intellectual disability. Prior psychiatric medication trials, each of which was prescribed for interfering symptoms of ADHD, included methylphenidate and dexmethylphenidate (both psychostimulants) which caused irritability, guanfacine (an alpha-2 adrenergic agonist) which caused sedation, and atomoxetine (a selective norepinephrine reuptake inhibitor) which caused lethargy and moodiness.

Three weeks prior to the initial evaluation, Ms. G had begun buspirone 2.5 mg every morning for anxiety. The medication had been mildly helpful for anxiety, so the dosage was gradually increased to 7.5 mg three times daily over a period of 6 months. Upon attaining the optimal dosage, Ms. G's mother reported that she had a > 70% improvement in anxiety and oppositional behaviors (Table 1). Ms. G has been maintained on buspirone 7.5 mg three times daily with no side effects for the past 6 years. She is now 15-year-old and is enrolled in a vocational high school. She no longer requires a 1:1 aide. She is enjoying school and has an active social life. Her anxiety is very well controlled, with only occasional mild anticipatory anxiety.

Case 3

Ms. M is a 19-year-old female with WS with an approximately twice normal sized deletion confirmed by single nucleotide polymorphism (SNP) array. She was the product

of a full-term, uncomplicated pregnancy. As an infant she had a poor suck reflex which caused difficulty feeding. In terms of developmental milestones, she sat at the age of 1 year and walked at the age of 3 years. She began babbling at 1 year of age, spoke her first word at 2 years of age, and began using two- to three-word phrases at 5 years of age. She demonstrated hand flapping and toe walking but no body rocking. She was fascinated with spinning objects and had an insistence on sameness. Her medical history is notable for recurrent episodes of otitis media resulting in eight sets of myringotomy tubes, pulmonary branch stenosis status post cardiac catheterization, mitral valve prolapse and regurgitation, mild supravalvular aortic stenosis, Chiari malformation status post surgical decompression, tethered spinal cord status post surgical correction, reactive airway disease, gastroesophageal reflux disease, periventricular heterotopia, and juvenile rheumatoid arthritis. She was attending a private, out of district, special education school where she was receiving physical, occupational, speech and music therapy.

At the time of initial evaluation at the age of 18 years, Ms. M's mother reported longstanding anxiety marked by a stressed facial expression with worsening over the past 6 months. She had begun waking up around 4 a.m. to engage in a number of behaviors which her mother believed were designed with the goal of avoiding school including unpacking her backpack, putting away food her mother had put out for her lunch, and taking out photos of family members and pointing to them as though she would like to go see them rather than go to school. Her anxiety and these behaviors were less severe on weekends. Ms. M's mother described her mood as happy, even, and content. She had no history of aggression, property destruction, or self-injurious behaviors. She enjoyed being around other people but would generally stay by herself among them which her mother believed was related to her reduced ability to communicate. She had no meaningful friendships. She had been taking citalopram 10 mg/day for the past 10 years which, until recently, had been very helpful for anxiety and sleep. Other prior psychiatric medication trials included melatonin which helped with sleep initiation but did not help with sleep maintenance and mirtazapine (a tetracyclic antidepressant) which caused increased appetite and aggression. There was a family history of anxiety in multiple maternal family members including Ms. M's mother, grandmother, and aunts and uncles. There was also a history of depression in her maternal aunts and uncles. Mental status exam was notable for limited verbal output and speaking in two- to three-word sentences, hand flapping, and flat affect.

Initial *DSM, 5th Edition* diagnoses included GAD and moderate intellectual disability. Ms. M was referred for neuropsychologic testing with a focus on assessing her capacity for vocational training. She was started on buspirone 2.5 mg each morning, which was increased at a rate of 2.5 mg per week given each morning and upon arriving home from school (3–4 p.m.). Citalopram was gradually tapered off to reduce polypharmacy with no worsening of symptoms of anxiety. Seven months later, Ms. M returned for follow-up. She was taking buspirone 7.5 mg twice daily, with a notable improvement in anxiety (Table 1). She was sleeping until 6 a.m., her facial expression appeared less worried, she was pacing less, and she was less resistant to completing tasks. She was tolerating buspirone well, without side effects. Due to residual symptoms of anxiety, her buspirone dose was further increased to 10 mg twice daily. Ms. M has continued on this dosage of buspirone for an additional 9 months with maintenance of her treatment response.

Discussion

This report describes the clinical presentation and use of buspirone for the treatment of anxiety in three adolescents/young adults with WS. Buspirone resulted in monotherapeutic improvement of anxiety and was well tolerated by all three patients, and in one of the cases, for many years.

Buspirone, a non-benzodiazepine, generally non-sedating anxiolytic, is a 5-HT_{1A} receptor partial agonist and D3/D4 antagonist. It has a Food and Drug Administration (FDA) indication for the treatment of GAD in adults. Multiple double-blind, placebo-controlled trials have demonstrated the efficacy of buspirone for treating symptoms of GAD in adults (Feighner et al. 1982; Pecknold et al. 1989; Sramek et al. 1997). Although rare, side effects can include headache, nausea, dizziness, and muscle tension (Schatzberg and DeBattista 2015). Buspirone typically requires twice per day dosing, due to its relatively short half-life of 1.6 h (Edwards et al. 2006). In these three cases, the maximal dose of buspirone required for efficacy in the WS population was 15 mg administered twice daily. The maximal total daily dosage of buspirone is typically 60 mg given in three divided doses.

The use of buspirone for the treatment of anxiety in individuals with WS has been minimally reported. A parent survey study of psychotropic medication usage among individuals with WS demonstrated that 30% had used buspirone. Sixty-four percent of patients who had taken buspirone found it either "helpful" or "somewhat helpful." (Martens et al. 2012) We previously described the effective use of buspirone for treating symptoms of post-traumatic stress disorder in a 9-year-old girl with WS (Alexander et al. 2019). The effect of buspirone on multiple target symptoms including anxiety, irritability, hyperactivity, and restricted/repetitive behaviors, has been described in other neurodevelopmental disorders, most notably in individuals with autism spectrum disorder (ASD). A case series of four children with ASD (ages 9 to 10 years) demonstrated that buspirone was associated with an improvement of at least one symptom

among hyperactivity, aggression, or stereotypy in three of four patients (Realmuto et al. 1989). A retrospective chart review demonstrated that treatment of 31 children with high-functioning ASD (ages 8 to 17 years) with co-morbid anxiety resulted in a significant change in mean Clinical Global Impressions Improvement (CGI-I) and Severity (CGI-S) scores. A significant improvement in anxiety symptoms was noted in 58% of patients, while mild improvement was observed in 29% of patients. Buspirone was generally well tolerated; behavioral activation and mood lability, respectively occurred in two patients (Ceranoglu et al. 2018). An open-label study of buspirone for the treatment of anxiety in children with pervasive developmental disorder showed that 16 of 21 (76%) children had a positive response which was sustained (Buitelaar et al. 1998). Finally, a double-blind, placebo-controlled, randomized clinical trial which included 166 children with ASD (ages 2 to 6 years) found that low-dose buspirone (2.5 mg twice daily) resulted in significant improvement in the Autism Diagnostic Observation Schedule Restricted and Repetitive Behavior score ($p = 0.03$). No difference were observed between the treatment and placebo groups in the ADOS Composite Total Score (Chugani et al. 2016).

The potential benefits of treatment with an anxiolytic medication must be carefully weighed against the potential risks among all patients, and especially those with WS. Classes of medications used to treat symptoms of GAD in the general population include benzodiazepines, SSRIs/serotonin and norepinephrine reuptake inhibitors (SNRIs), antihistamines, and first and second generation antipsychotics. Adverse effects associated with benzodiazepine use include sedation, respiratory suppression, dependence, and withdrawal (Schatzberg and DeBattista 2015). Furthermore, epidemiological studies have demonstrated higher rates of dementia among benzodiazepine users (Pariente et al. 2016). In contrast to benzodiazepines, buspirone is well tolerated by medically ill patients, does not cause respiratory suppression, can be tapered relatively quickly without risk of withdrawal, and does not affect cognition (Schatzberg and DeBattista 2015). The lack of cognitive side effects is of particular relevance in patients with WS due to the high rate of intellectual disability. SSRIs and SNRIs are among first-line medication options for the treatment of GAD in the general population. Currently, escitalopram and paroxetine (both SSRIs), and venlafaxine (a SNRI), have an FDA indication for the treatment of GAD in adults. Although SSRIs and SNRIs are generally well tolerated, there is a paucity of research on the efficacy and tolerability of SSRIs and SNRIs in individuals with WS. Common side effects of SSRIs and SNRIs include GI side effects (nausea, diarrhea, heart-burn), sexual dysfunction, headache, and insomnia (Schatzberg and DeBattista 2015). A national survey study of 513 children and adults with WS demonstrated that 24% of individuals with WS had been prescribed at least one SSRI. Overall, 81% of individuals who had taken a SSRI reported that it had been either helpful or somewhat helpful (Martens et al. 2012). However, larger, controlled studies assessing the safety and efficacy of SSRIs and SNRIs among individuals with WS are lacking. Antihistamines, such as diphenhydramine and hydroxyzine, are also used to treat symptoms of GAD in the general population. Daily, long-term use of antihistamines is limited by their sedating effects (Guaiana et al. 2010) and anticholinergic side effects including dry mouth, dry eyes, urinary retention, constipation, and impaired cognition (Schatzberg and DeBattista 2015). As mild to moderate intellectual disability is common among individuals with WS, it is prudent to avoid medications which can negatively affect cognition. First and second generation antipsychotic medications are also considered for the treatment of severe anxiety. A case series including two adult patients with WS reported that use of low doses of a low-potency first generation antipsychotic (levomepromazine) was helpful for the treatment of insomnia and anxiety. Both patients in this case series subsequently developed depressive symptoms which responded to a SSRI. (Urgeles et al. 2013) Second, and at times first generation antipsychotic medications are associated with metabolic side effects, including weight gain, dyslipidemia, hyperglycemia, and hypertension (Solmi et al. 2017). Adverse metabolic effects can be of particular concern among individuals with WS, as the prevalence of metabolic impairment is unusually high. Two-thirds of patients with WS have a body mass index (BMI) of > 25, 75% have glucose intolerance or diabetes mellitus, and hypertension develops in approximately 50% of patients with WS (Pober 2010). In contrast to first and second generation antipsychotics, buspirone is not known to be associated with adverse metabolic effects. In addition to metabolic side effects, nearly all first and second generation antipsychotics have the potential to cause significant cardiac effects including prolongation of the electrocardiographic QTc interval which increases the risk for a life-threatening ventricular arrhythmia (Beach et al. 2018). Prolonged QTc (> 460 ms) is more common among individuals with WS (Collins et al. 2010). Importantly, buspirone has not been reported to prolong the QTc interval (Wenzel-Seifert et al. 2011). Supravalvular aortic stenosis, which occurs in approximately 70% of WS patients, and other cardiovascular complications are a major cause of death in this population (Pober 2010). In sum, buspirone's generally benign side effect profile is a major benefit of its use for treating GAD in individuals with WS.

There are several limitations to this report. All treatments were open-label and there was no control group. Standardized assessments of treatment outcomes were not performed prospectively. Rather, assessment of clinical improvement was ascertained by clinical observations as well as the retrospective administration of the Pediatric Anxiety Rating

Scale (PARS) to each mother (Table 1). ("PARS: Development and psychometric properties" 2002) Additionally, in some cases patients received psychotherapy, optimization of medical conditions (e.g. constipation), and changes in the school or living environment in conjunction with buspirone. Thus, it is possible that clinical improvement may have been at least in part, the result of these other interventions. Finally, this report is limited by the small sample size. Future larger scale studies on the safety, tolerability, and efficacy of buspirone for the treatment of anxiety in individuals with WS are warranted.

This case series describes symptoms of GAD in three adolescents/young adults with WS and their course of treatment with buspirone. Comorbid anxiety in WS is highly prevalent, persistent, and can greatly impact quality of life. It can be challenging to ascertain whether anxiety is present in an individual with developmental disabilities, particularly if expressive language and cognition is impaired. It can be helpful to assess facial expression and behaviors, and obtain collateral information from caregivers, teachers, employers, and family members. It is important that clinicians treating individuals with WS assess for the presence of co-morbid anxiety disorders, including GAD, and consider a trial of a medication with low risk for sedation, metabolic effects, and dependence, such as buspirone.

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Author Contributions RPT, CJK and CJM drafted the manuscript. CJM performed the ratings of the Pediatric Anxiety Rating Scale with the mother of each subject. RPT, CJK, JLW, BRP and CJM reviewed the final version of the manuscript and gave approval for its submission.

Compliance with Ethical Standards

Conflict of interest Drs. Thom, Pober and McDougle and Ms. Waxler declare that they have no conflicts of interest. Dr. Keary has been a compensated consultant, served on a scientific advisory board and received research support from Ovid Therapeutics.

Informed Consent Informed consent was obtained from the legal guardian of all individual participants included in the study.

Research Involving Human Participants and/or Animals The study was granted exemption from requiring ethics approval by the Partners Human Research Committee Institutional Review Board because the number of subjects included in the study is less than four.

References

Alexander, A., Gallagher, A., Pober, B., Waxler, J., & McDougle, C. (2019). Post-traumatic stress disorder following cardiac surgery: A case report of a nine-year-old female with Williams syndrome. *Journal of Intellectual & Developmental Disability, 44*(2), 244–247.

Beach, S. R., Celano, C. M., Sugrue, A. M., Adams, C., Ackerman, M. J., Noseworthy, P. A., et al. (2018). QT prolongation, Torsades de Pointes, and psychotropic medications: A 5-year update. *Psychosomatics, 59*(2), 105–122. https://doi.org/10.1016/j.psym.2017.10.009.

Bergman, J., Roof, R. A., Furman, C. A., Conroy, J. L., Mello, N. K., Sibley, D. R., et al. (2013). Modification of cocaine self-administration by buspirone (buspar®): Potential involvement of D3 and D4 dopamine receptors. *International Journal of Neuropsychopharmacology, 16*(2), 445–458. https://doi.org/10.1017/S1461145712000661.

Buitelaar, J. K., van der Gaag, R. J., & van der Hoeven, J. (1998). Buspirone in the management of anxiety and irritability in children with pervasive developmental disorders: Results of an open-label study. *The Journal of Clinical Psychiatry, 59*(2), 56–59.

Ceranoglu, T. A., Wozniak, J., Fried, R., Galdo, M., Hoskova, B., Fong, M. D., et al. (2018). A retrospective chart review of buspirone for the treatment of anxiety in psychiatrically referred youth with high-functioning autism spectrum disorder. *Journal of Child and Adolescent Psychopharmacology*. https://doi.org/10.1089/cap.2018.0021.

Chugani, D. C., Chugani, H. T., Wiznitzer, M., Parikh, S., Evans, P. A., Hansen, R. L., et al. (2016). Efficacy of low-dose buspirone for restricted and repetitive behavior in young children with autism spectrum disorder: A randomized trial. *The Journal of Pediatrics, 170*(45–53), e1–e4. https://doi.org/10.1016/j.jpeds.2015.11.033.

Collins, R. T. (2018). Cardiovascular disease in Williams syndrome. *Current Opinion in Pediatrics, 30*(5), 609–615. https://doi.org/10.1097/MOP.0000000000000664.

Collins, R. T., Aziz, P. F., Gleason, M. M., Kaplan, P. B., & Shah, M. J. (2010). Abnormalities of cardiac repolarization in Williams syndrome. *The American Journal of Cardiology, 106*(7), 1029–1033. https://doi.org/10.1016/j.amjcard.2010.05.041.

Dykens, E. M. (2003). Anxiety, fears, and phobias in persons with Williams Syndrome. *Developmental Neuropsychology, 23*(1–2), 291–316. https://doi.org/10.1080/87565641.2003.9651896.

Edwards, D. J., Chugani, D. C., Chugani, H. T., Chehab, J., Malian, M., & Aranda, J. V. (2006). Pharmacokinetics of buspirone in autistic children. *The Journal of Clinical Pharmacology, 46*(5), 508–514. https://doi.org/10.1177/0091270006286903.

Ewart, A. K., Morris, C. A., Atkinson, D., Jin, W., Sternes, K., Spallone, P., et al. (1993). Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. *Nature Genetics, 5*(1), 11–16. https://doi.org/10.1038/ng0993-11.

Feighner, J. P., Merideth, C. H., & Hendrickson, G. A. (1982). A double-blind comparison of buspirone and diazepam in outpatients with generalized anxiety disorder. *The Journal of Clinical Psychiatry, 43*(12 Pt 2), 103–108.

Guaiana, G., Barbui, C., & Cipriani, A. (2010). Hydroxyzine for generalised anxiety disorder. *Cochrane Database of Systematic Reviews, 12,* CD006815. https://doi.org/10.1002/14651858.cd006815.pub2.

Kim, Y.-M., Cho, J. H., Kang, E., Kim, G.-H., Seo, E.-J., Lee, B. H., et al. (2016). Endocrine dysfunctions in children with Williams-Beuren syndrome. *Annals of Pediatric Endocrinology & Metabolism, 21*(1), 15–20. https://doi.org/10.6065/apem.2016.21.1.15.

Leyfer, O. T., Woodruff-Borden, J., Klein-Tasman, B. P., Fricke, J. S., & Mervis, C. B. (2006). Prevalence of psychiatric disorders in 4 to 16-year-olds with Williams syndrome. *American Journal of Medical Genetics Part B, Neuropsychiatric Genetics: The Official Publication of the International Society of Psychiatric Genetics, 141B*(6), 615–622. https://doi.org/10.1002/ajmg.b.30344.

Martens, M. A., Seyfer, D. L., Andridge, R. R., Foster, J. E. A., Chowdhury, M., McClure, K. E., et al. (2012). Parent report of antidepressant, anxiolytic, and antipsychotic medication use in individuals with Williams syndrome: Effectiveness and adverse effects.

Research in Developmental Disabilities, 33(6), 2106–2121. https://doi.org/10.1016/j.ridd.2012.06.006.

Martens, M. A., Wilson, S. J., & Reutens, D. C. (2008). Research Review: Williams syndrome: a critical review of the cognitive, behavioral, and neuroanatomical phenotype. *Journal of Child Psychology and Psychiatry, 49*(6), 576–608. https://doi.org/10.1111/j.1469-7610.2008.01887.x.

Mervis, C. B., Robinson, B. F., Bertrand, J., Morris, C. A., Klein-Tasman, B. P., & Armstrong, S. C. (2000). The Williams syndrome cognitive profile. *Brain and Cognition, 44*(3), 604–628. https://doi.org/10.1006/brcg.2000.1232.

Morris, C. A. (1993). *Williams Syndrome*. *GeneReviews®*. Retrieved January 23, 2019, from http://www.ncbi.nlm.nih.gov/pubmed/20301427.

Pariente, A., de Gage, S. B., Moore, N., & Bégaud, B. (2016). The benzodiazepine-dementia disorders link: Current state of knowledge. *CNS Drugs, 30*(1), 1–7. https://doi.org/10.1007/s40263-015-0305-4.

Pecknold, J. C., Matas, M., Howarth, B. G., Ross, C., Swinson, R., Vezeau, C., et al. (1989). Evaluation of buspirone as an antianxiety agent: Buspirone and diazepam versus placebo. *Canadian Journal of Psychiatry. Revue canadienne de psychiatrie, 34*(8), 766–771.

Pober, B. R. (2010). Williams-Beuren syndrome. *The New England Journal of Medicine, 362*(3), 239–252. https://doi.org/10.1056/NEJMra0903074.

Realmuto, G. M., August, G. J., & Garfinkel, B. D. (1989). Clinical effect of buspirone in autistic children. *Journal of Clinical Psychopharmacology, 9*(2), 122–125.

Royston, R., Howlin, P., Waite, J., & Oliver, C. (2017). Anxiety disorders in Williams syndrome contrasted with intellectual disability and the general population: A systematic review and meta-analysis. *Journal of Autism and Developmental Disorders, 47*(12), 3765–3777. https://doi.org/10.1007/s10803-016-2909-z.

Schatzberg, A., & DeBattista, C. (2015). *Manual of clinical psychopharmacology* (8th ed.). Arlington, VA: American Psychiatric Publishing Inc.

Solmi, M., Murru, A., Pacchiarotti, I., Undurraga, J., Veronese, N., Fornaro, M., et al. (2017). Safety, tolerability, and risks associated with first- and second-generation antipsychotics: A state-of-the-art clinical review. *Therapeutics and Clinical Risk Management, 13,* 757–777. https://doi.org/10.2147/TCRM.S117321.

Sramek, J. J., Frackiewicz, E. J., & Cutler, N. R. (1997). Efficacy and safety of two dosing regimens of buspirone in the treatment of outpatients with persistent anxiety. *Clinical Therapeutics, 19*(3), 498–506.

Strømme, P., Bjømstad, P. G., & Ramstad, K. (2002). Prevalence estimation of Williams syndrome. *Journal of Child Neurology, 17*(4), 269–271. https://doi.org/10.1177/088307380201700406.

The Pediatric Anxiety Rating Scale (PARS): Development and psychometric properties. (2002). *Journal of the American Academy of Child and Adolescent Psychiatry*, *41*(9), 1061–1069. Retrieved August 19, 2019, from http://www.ncbi.nlm.nih.gov/pubmed/12218427.

Urgeles, D., Alonso, V., & Ramos-Moreno, T. (2013). Neuropsychiatric and behavioral profiles of 2 adults with Williams syndrome: Response to antidepressant intake. *Primary Care Companion to the Journal of Clinical Psychiatry*. https://doi.org/10.4088/pcc.13m01504.

Wenzel-Seifert, K., Wittmann, M., & Haen, E. (2011). QTc prolongation by psychotropic drugs and the risk of Torsade de Pointes. *Deutsches Arzteblatt International, 108*(41), 687–693. https://doi.org/10.3238/arztebl.2011.0687.

Woodruff-Borden, J., Kistler, D. J., Henderson, D. R., Crawford, N. A., & Mervis, C. B. (2010). Longitudinal course of anxiety in children and adolescents with Williams syndrome. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics, 154C*(2), 277–290. https://doi.org/10.1002/ajmg.c.30259.